

## REMARKS

### I. Status of the Claims

Claims 59-67 and 77-78 are pending. Claim 77 is amended to point out that the endothelial cell/smooth muscle cell/matrix combination is cultured only after it is positioned around the tubular support. Support for this can be found, inter alia, in the paragraph spanning pages 17-18 and Example 2, page 33, of the Applicants' specification.

### II. The Rejections

#### A. Rejection Under 35 U.S.C. § 112, Second Paragraph

This rejection is moot as Applicants sought to cancel the claim in their reply to the Final Office Action and the Examiner indicated in the Advisory Action that the amendment would be entered. Accordingly, claim 76 has been canceled. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

#### B. Double Patenting

This issue is moot as Applicants sought to cancel both of the claims in their reply to the Final Office Action and the Examiner indicated in the Advisory Action that the amendment would be entered.

#### C. Rejection Under 35 U.S.C. § 102(b)

On page 4 of the final Office Action, claims 59-67 and 76 are rejected on the grounds that they are anticipated by Niklason (*Science*, 1999) in light of Henrikson (*Histology*, 1997) and Freshney (*Culture of Animal Cells: A Manual of Basic Technique*, 2000). This rejection is moot as Applicants sought to cancel all of these claims (without acquiescing in the propriety of this rejection) in their reply to the Final Office Action and the Examiner indicated that the amendment would be entered. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

D. Rejection Under 35 U.S.C. § 103(a)

1. Rejection over Niklason in light of Henrikson and Freshney and in view of Tu  
(U.S. Patent 6,506,398)

On page 8 of the final Office Action, claims 68-76 are rejected under 35 U.S.C. § 103(a) on the grounds that they are unpatentable over Niklason in light of Henrikson and Freshney and in view of Tu. First, Applicants point out that the Office Action appears to contain a typographical error by including claim 77. In the discussion of the particulars of the rejection on page 8, the Examiner does not discuss method claim 77. In fact, the only additional reference is that of Tu and this is cited only for teaching VEGF. Since claim 77 was not rejected as anticipated by Niklason, Applicants do not address claim 77 with respect to this § 103 rejection. In any event, as to the remainder of the claims, Applicants respectfully submit that the rejection is moot as Applicants sought to cancel all of the claims (with the exception of claim 77) in their reply to the Final Office Action and the Examiner indicated that the amendment would be entered. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

2. Rejection over Shum-Tim in light of Henrikson and taken in view of Dunkelman  
and further in view of Mitchell and Hall

On page 9 of the final Office Action, method claims 59-67 and 77 are rejected on the grounds that they are obvious over Shum-Tim et al., *Ann Thorac Surg* (1999), in light of Henrikson, and taken in view of Dunkelman et al. (U.S. Patent 5,792,603), and further in view of Mitchell et al., *Cardiovascular Pathol* (2003) and Hall et al. (U.S. Patent 6,387,663). Applicants respectfully traverse the rejection.

Shum-Tim, the primary reference, is relied upon as follows:

Shum-Tim et al disclose development of tissue-engineered vascular graft comprising seeding a mixture of endothelial cells, smooth muscle cells and fibroblasts onto a polymeric scaffold. The cells are cultured on the scaffold for seven days, and then implanted as an aortic replacements.

In the method of Shum-Tim et al the polymeric scaffold is considered to read on the matrix of the claimed invention. The cells are seeded onto the matrix as a mixed population, thus none of the cells are cultured on the matrix or contacted with any growth factors prior to all cells being present on the matrix.

**Shum-Tim et al differs from the instant invention in that they do not disclose details of the seven day culture period which occurs after cell seeding and before implantation of the tissue-engineered vascular graft. Specifically, Shum-Tim et al do not disclose circumferentially positioning the cell-seeded matrix around a tubular support, through which one or more factors are contained, and culturing thereupon.**

Emphasis added.

The Examiner cites pages 2298 and 2299. Page 2298 explains the history of using a PGA copolymer scaffold to deliver cells. The improvement of Shum-Tim is adding an outer layer of a PHA copolymer that has a long degradation time and withstands systemic pressure. The PGA part forms an inner layer matrix for cell attachment and growth. The outer component is made of three layers of "non-porous" PHA. This polymer has high tensile strength. This tubular conduit is "completely impermeable to fluid." According to the reference, the PHA layer provides the necessary biomechanical characteristics of the tubular scaffold as the cells lay down their own extracellular matrix on the PGA surface. Eventually, both layers degrade *in vivo*, leaving the engineered cells in a tubular shape, having produced their own extracellular matrix.

Accordingly, Shum-Tim fails to teach or suggest applying the cells and matrix to the outside of the tubular support. In fact, if that were done, that would defeat the purpose of the tubular support, which is to provide a structure to protect the inner cells and matrix so that they form a structure sufficiently integrated to function *in vivo*. Furthermore, Shum-Tim does not teach or suggest a porous tubular support. The support is impermeable. If liquid could have flowed through the layers, this would have disrupted the formation of the integrated inner tube. Thus, the reference is deficient in teaching these two features.

The Examiner acknowledges that Shum-Tim does not teach positioning the cells and matrix around a porous tubular support. But, the Examiner takes the position that this “deficiency” would be compensated “by combining the cell-seeded matrix of Shum-Tim with the Dunkelman apparatus.”

The Examiner relies on Dunkelman as follows:

**It is submitted that one of ordinary skill in the art would have found it prima facie obvious to use the apparatus of Dunkelman et al to carry out the seven day culture of the cell-seeded polymer scaffold in the method of Shum-Tim et al. The rationale for this conclusion of obviousness is that means for enhancing a particular method (the culture method of Shum-Tim et al.) has been made part of the ordinary capabilities of one of skill in the art based upon the teachings of such improvements in other situations (specifically the perfusion system of Dunkelman et al.)...and the results would have been predictable...specifically: successful development of the tissue engineered vascular graft of Shum-Tim et al.**

Emphasis added.

Thus, the Examiner asserts that it would have been obvious to apply the cell-seeded polymer scaffold of Shum-Tim to the porous tubular support of Dunkelman for the seven-day culture period because it would enhance the Shum-Tim method.

In their response to the final Office Action, Applicants explained that the Dunkelman method would be detrimental to making the Shum-Tim graft because the cells in the seeded graft are not sufficiently attached. Shum-Tim specifically teaches the necessity of a seven-day period for sufficient attachment and that is in static culture. In the Dunkelman apparatus, there is constant liquid flow under pressure (non-static culture). Because of this, motivation to combine would have been lacking, there would have been no reasonable expectation of success, and, even if the references were combined, one would not have achieved the claimed invention.

On page 3 of the Advisory Action, the Examiner asserted that “within a matter of hours cells would be expected to have established sufficient attachment so as to operation [sic] of the device of Dunkelman.”

Without addressing the factual accuracy of that assertion, Applicants point out that claim 77 is amended to recite that the endothelial cells, smooth muscle cells, and matrix are not cultured together until the combination is positioned on the exterior surface of the tubular support. Thus, there would have been no opportunity for the cells to attach.

### Three Requirements to Support the Rejection

To support a rejection under 35 U.S.C. § 103 based on a combination of references, there are three requirements. First, there must be a motivation to combine the references. Second, there must be a reasonable expectation of success that the claimed invention will result from combining the references. Third, combining the references must produce the actual claimed invention. In the present case, none of these requirements is met.

### No Motivation to Apply the Seeded Scaffold to Dunkelman's Porous Tube

The rationale for combining references is based on the supposition that applying the vascular graft of Shum-Tim to the Dunkelman apparatus for the seven day culture period would be an "enhancement" of the Shum-Tim method. How it would enhance the method is not explained. Applicants submit that it would not enhance the method for the reasons explained below.

Applicants point out that to do this would, in fact, be detrimental to the Shum-Tim method. When the cells are introduced into the lumen, they do not immediately attach. Therefore, Shum-Tim teaches a seven-day culture period for the seeded cells to attach to and incorporate into the PGA scaffold. The authors indicate that seven days was "usually sufficient" for the seeded cells to become attached and confluent on the polymer surface.

If one were to apply Shum-Tim's seeded matrix to the Dunkelman porous tube, this would disrupt attachment. The unattached cells would be lost by physical dispersion. So, it would defeat the Shum-Tim

method. For this reason alone, the person of ordinary skill in the art would not have been motivated to perform the seven-day culture on the seeded graft of Shum-Tim in the Dunkelman apparatus.

No Reasonable Expectation that the Sum-Tim Graft Could be Produced if the Seeded Graft is Layered on the Dunkelman Tube

Second, because the cells are not attached to the matrix in the Shum-Tim seeded construct and would have been washed away in the Dunkelman apparatus, had one thought to apply the seeded graft to the Dunkelman tube, there would have been no reasonable expectation that one would have successfully made the Shum-Tim final construct.

Combination of References Does Not Result in Claimed Method

Third, if one had combined the references, they would not have achieved the claimed invention. They could not have grown the combination of endothelial cells, smooth muscle cells, and matrix on the exterior surface of the tubular support because those cells would be lost in the Dunkelman apparatus.

Therefore, none of the three requirements to sustain a rejection under 35 U.S.C. § 103 for combining references is met.

Declaration of Dr. Robert T. Tranquillo

In addition to, and independent of, the arguments presented above, Applicants point out that the claims require that culturing the factors with the matrix/endothelial cells/smooth muscle cells that are circumferentially positioned around the tubular support results in the formation of an endothelial intimal layer surrounded by a smooth muscle medial layer. This requirement is found in previously presented claim 59 and in new claim 78. Doctor Tranquillo explains why, even if, as the Examiner suggests, the Shum-Tim graft was placed on the Dunkelman apparatus, this requirement would not be met. In short, Dr. Tranquillo explains that, as the specification teaches, the purpose for the chemo-attractants and/or mitogens in the lumen of the claimed vascular construct is for diffusion into the construct, establishing a concentration gradient, and inducing the endothelial cells to localize to the surface by chemotaxis and/or

proliferation. Accordingly, establishing a sufficient concentration gradient within the construct, as taught by the specification, results in the formation of the two layers. He explains that the Dunkelman process involves pressurizing the fluid in the lumen to result in convective flow outward through the construct. This is termed "transmural flow." This would undermine establishing the gradients of attractants and/or mitogens that would lead to the formation of the two layers. Accordingly, the Examiner is directed to Dr. Tranquillo's Declaration.

#### Summary

The Examiner takes the position that the motivation would have been to improve the Shum-Tim method and that the results would have been predictably successful. But, altering the Shum-Tim procedure by layering the seeded graft around the Dunkelman porous tube would have interfered with the effective functioning of the Shum-Tim method. The person of ordinary skill in the art reasonably would have predicted that layering this graft around the Dunkelman tube would interfere with cell attachment and growth to confluency. Moreover, as is explained by Dr. Tranquillo, the Dunkelman apparatus would prevent the formation of an endothelial intimal layer surrounded by a smooth muscle medial layer. Thus, there would have been no motivation to combine, no reasonable expectation of success, and no actual claimed invention even if the references had been combined.

In view of the above arguments and/or amendment, Applicants submit that the grounds of rejection have been addressed and the rejection overcome. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

#### IV. Conclusion

In view of Applicants' discussion, Applicants believe that the pending claims are in condition for allowance. Early notification to that effect is respectfully requested.

Applicants believe that fees for a five-month extension of time are due with this filing. Such payment is being made simultaneously with the filing of this paper via Electronic Funds Transfer. The Commissioner is authorized to charge any deficiencies, or credit any overpayment, to our Deposit Account No. 20-0809. Applicants hereby authorizes the Commissioner under 37 C.F.R. §1.136(a)(3) to treat any paper that is filed in this application which requires an extension of time as incorporating a request for such an extension.

Respectfully submitted,



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